STUDY PROTOCOL: Lipids, inflammation, and cardiovascular risk in rheumatoid arthritis

NCT02714881

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Objective

The objective of this study is to elucidate the relationship between inflammation and lipoprotein atherogenicity, and to determine the relative contribution of inflammation and lipids to cardiovascular (CV) risk in RA. Our central hypothesis is that inflammation and lipoprotein atherogenicity is tightly linked such that both factors are important to assess CV risk in RA. Further, we hypothesize that this relationship is obscured by a consideration of routine lipids alone.

Study population and design

The Lipids, Inflammation and CV Risk in RA (LiiRA, ClinicalTrials.gov: NCT02714881) study conducted from 2016 to 2021, prospectively enrolled RA patients, age>35, with active RA with a plan to initiate tumor necrosis factor inhibitor (TNFi) therapy as directed by their treating rheumatologist. Exclusion criteria include prior cardiovascular disease, statin use, prednisone dose or equivalent >10mg, or biologic DMARD use in the past 24 weeks. All subjects underwent PET myocardial perfusion imaging (MPI) at baseline, were initiated on a TNFi, and returned for study visits at 6, 12 and 24 weeks, where a repeat PET MPI was performed. At each study visit, subjects had assessment of RA disease activity, current RA therapy, and screening for adverse events. Blood draws were also performed for measurements of fasting lipids, inflammatory markers and subclinical markers of myocardial injury.

A control group of healthy subjects with similar age and sex from our prior work using the same imaging protocol and quantitative analysis of myocardial perfusion PET images was also included to compare baseline imaging findings in the RA cohort. Inclusion criteria for this study were patients without a history or clinical evidence of CAD.

Assessment of myocardial blood flow and flow reserve

Myocardial blood flow was measured at rest and during maximal hyperemia using 15-20 mCi of ^{13}N-ammonia as the flow tracer and a whole-body PET/CT scanner (Discovery RX or MI LightSpeed 64, GE Healthcare, Wakesha, WI). Low dose CT scans were used for attenuation correction and for semi-quantitative visual assessment of coronary artery calcification. Coronary artery calcium (CAC) was categorized as absent, mild (1-99), moderate (100-299), and severe (≥ 300). This semi-quantitative visual assessment correlates well with the Agatston score. Maximal hyperemia was achieved using regadenoson as per standard care. Patients were asked to refrain

from caffeinated products for 12 hours, theophylline-containing and arterial vasodilator medications the day of the study.

A semiquantitative 17-segment visual assessment using a standard 5-point scoring system was used to evaluate for myocardial ischemia and scar. Absolute MBF was computed from the rest and stress myocardial perfusion PET images using commercially available software (Corridor4DM; Ann Arbor, Michigan) and a two-compartment tracer kinetic model. All images were motion corrected and analyzed in a blinded fashion. Intrareader and inter-reader variability from our laboratory have previously been published. MFR was calculated as the ratio of stress over rest myocardial blood flow. All reported MBF and MFR values indicate global measure. MFR was calculated as the ratio of stress over rest myocardial blood flow. Rest MBF was also normalized by the rest rate-pressure product, an index of cardiac work, by dividing rest flow by the resting rate pressure product and multiplied by 10,000[22]. Corrected MFR was defined as stress MBF divided by corrected rest MBF. All reported MBF and MFR values indicate global measure.CMD was defined as a MFR <2.5, reflecting mild coronary microvascular dysfunction, based on prior work.

Effect of reducing inflammation on CMD, primary cohort

A TNFi, specifically certolizumab was used as the intervention to reduce inflammation. TNFi's are the most commonly used treatment after inadequate response to the first line therapy methotrexate for RA. Per our protocol, subjects were allowed to switch to other treatments if certolizumab was inadequate in controlling RA disease activity at the discretion of their treating rheumatologist with the overall goal to control inflammation.

The study was designed to enroll 75 subjects with an expectation anticipating 25% loss to follow-up with an anticipated of n=66 subjects completing the study. The study ultimately recruited 74 subjects with 66 subjects completing the study. As this study was initiated prior and enrolled through the COVID-19 pandemic, subjects' follow-up times extended beyond 24 weeks; this modification was approved by the Mass General Brigham Institutional Review Board. All patients were enrolled from rheumatology practices at Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts General Hospital, Boston, MA and Mount Auburn Hospital, Cambridge, MA. All PET MPI was performed at Brigham and Women's Hospital.

Study Outcomes and Measures

The primary outcome was the change in global MFR after 24 weeks of treatment starting with TNFi therapy. MFR, the ratio of peak vasodilator stress to rest MBF, represents the maximal ability to augment coronary flow and myocardial perfusion. The secondary outcome was change in hs-cTnT at baseline and 24 weeks. Inflammatory marker and hs-cTnT measurement was also available for baseline, week 6, 12 and 24 weeks.

Inflammatory biomarkers

Blood biomarkers were measured and broadly categorized into clinically measured acute phase reactants and inflammatory pathways implicated in RA or CVD. The acute phase reactants included: erythrocyte sedimentation rate (ESR) and high sensitivity C-reactive protein (hsCRP), measured using clinical assays. The remainder of the biomarkers were measured at Children's Hospital as previously described. Inflammatory pathways implicated in RA or CVD comprised of IL-1a, IL-1b, IL-6, and sTNFR2. Inflammatory biomarkers without clinical cut-off values were categorized into tertiles. Changes in biomarkers were also categorized into tertiles.

Clinical measurements

RA Disease Activity was assessed using the validated disease activity score (DAS)28-CRP with 3 components. DAS28-CRP3 incorporates the 28 tender and swollen joint count and hsCRP. We additionally calculated the clinical disease activity index (CDAI), which does not include hsCRP in the calculation.

Statistical Analysis

Means and standard deviations were used to describe most continuous variables, medians and IQRs were used to describe variables with non-normal distributions, and frequency and percent were used to describe categorical variables. Comparison p-values for outcome variables and other variables before and after TNFi therapy were computed using paired t-tests or the Wilcoxon signed rank test for non-normally distributed variables. Spearman's correlation was used to test the correlation between the log of baseline inflammatory markers and the primary outcome, MFR, and secondary outcome, hs-cTnT. As well, Spearman's correlation was used to test the relationship between change in inflammation and the primary and secondary outcomes. An exploratory subgroup analysis was also performed to test the correlation between change in inflammatory markers with change in hs-cTnT, among subjects with CMD (MFR<2.5) at baseline and 24 weeks. As measurements were available for inflammatory markers and hs-cTnT at

multiple time points, we additionally tested the association between the inflammatory markers with hs-cTnT over time.